Paroxysmal Nocturnal Hemoglobinuria

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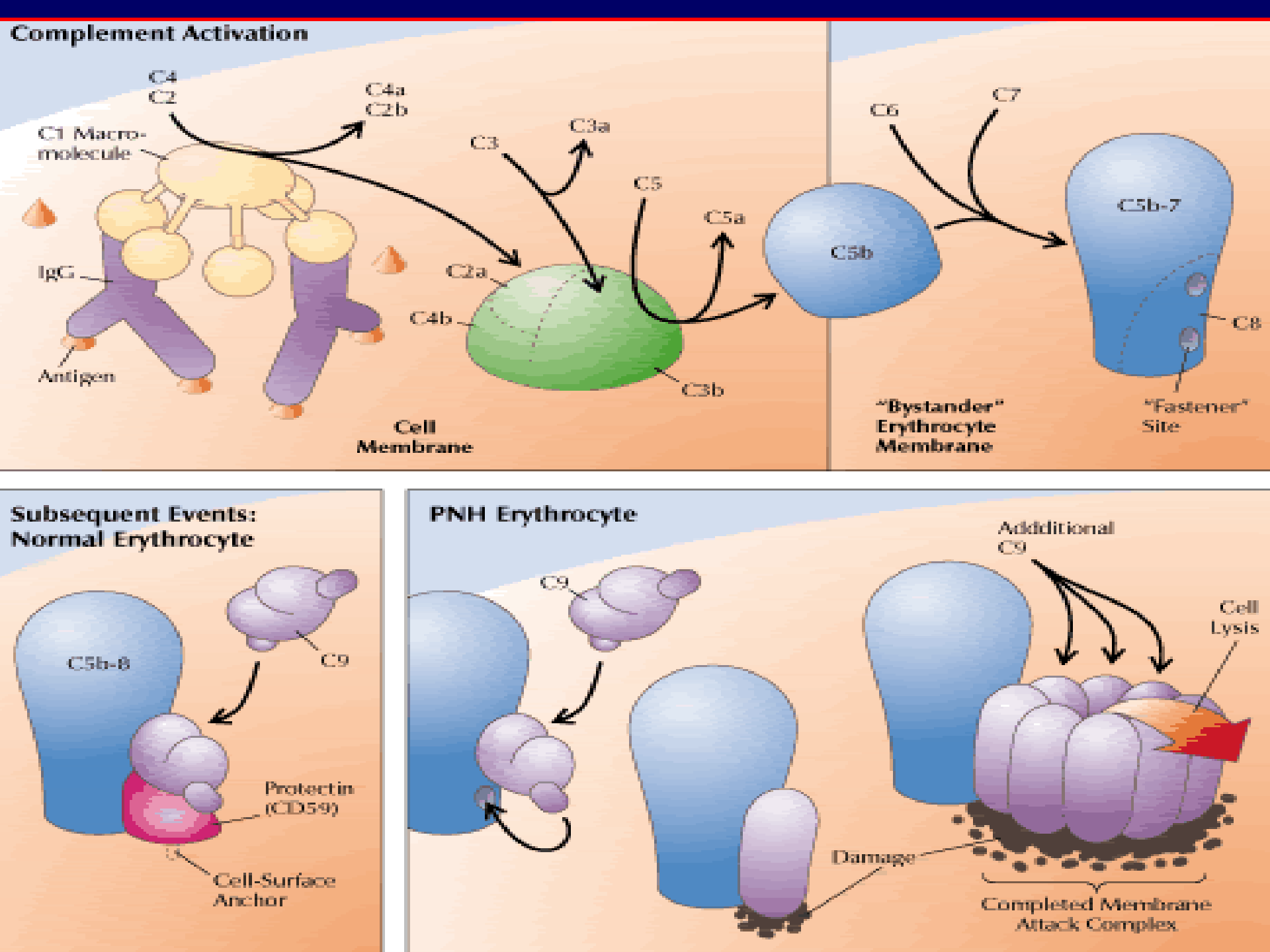
- Rare acquired hematopoetic stem cell disorder
- 1-10 per million
- Most frequent in 3rd decade
- Asian ancestry
- RBCs susceptible to complement-mediated lysis
- Related to lack of cell surface proteins that prevent complement attack

History of PNH

- **1866**—first case report by Gull describing nocturnal hematuria
- **1882—**Strubing recognized PNH as a definite syndrome
- **1925**—Enneking coined the name “Paroxysmal Nocturnal Hemoglobinuria”
- **1930s**—Ham identified the role of complement and developed the serum test which is still used for diagnosis
- **1980s—**PNH blood cells found to lack cell surface proteins
- **1990s—**Somatic mutation identified as *PIG-A* gene


Complement Activation
C4
C2
C4a
C2b
C1 Macro-molecule
C3
C3a
C5
C5a
C6
C7
C5b
C5b-7
IgG
C2a
C4b
C8
Antigen
C3b
Cell Membrane
"Bystander" Erythrocyte Membrane
"Fastener" Site
Subsequent Events: Normal Erythrocyte
C5b-8
C9
Protectin (CD59)
Cell-Surface Anchor
PNH Erythrocyte
C9
Additional C9
Cell Lysis
Damage
Completed Membrane Attack Complex

Pathophysiology of PNH

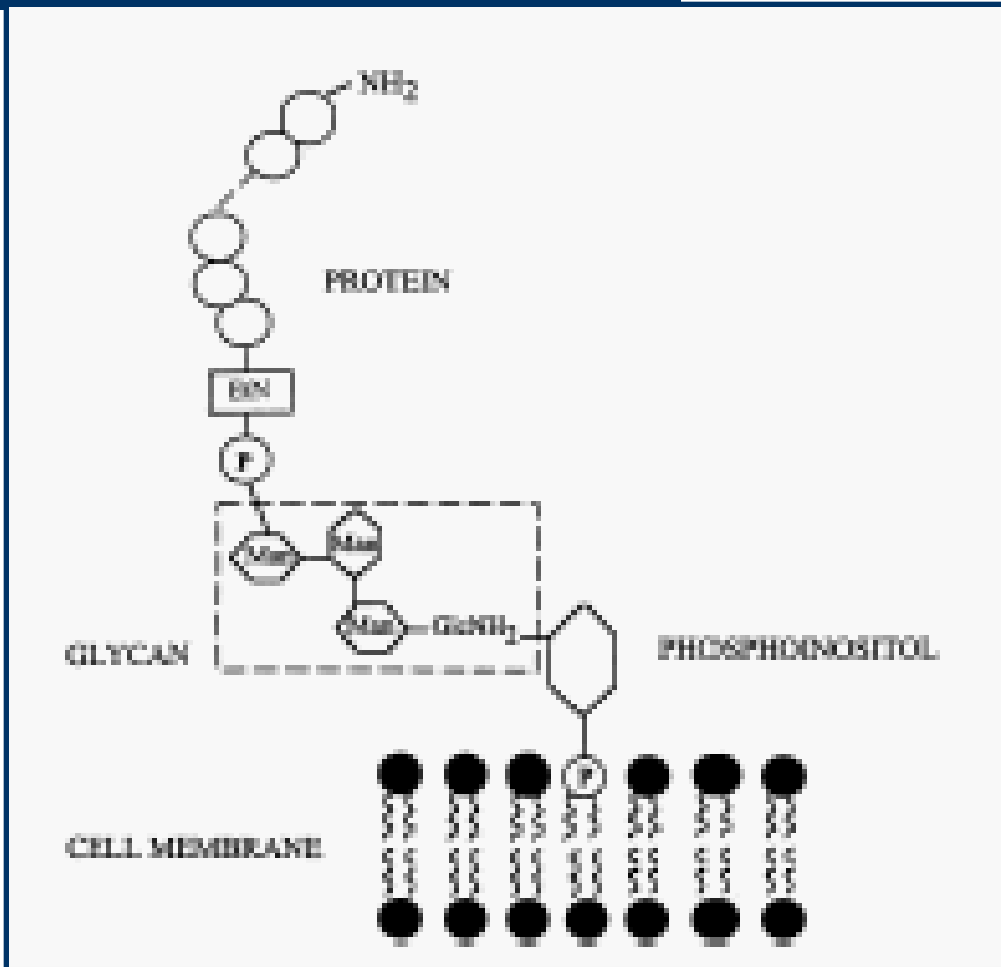
- **Attachment of cell surface proteins**
  - transmembrane hydrophobic sequence
  - anchor embedded within the membrane

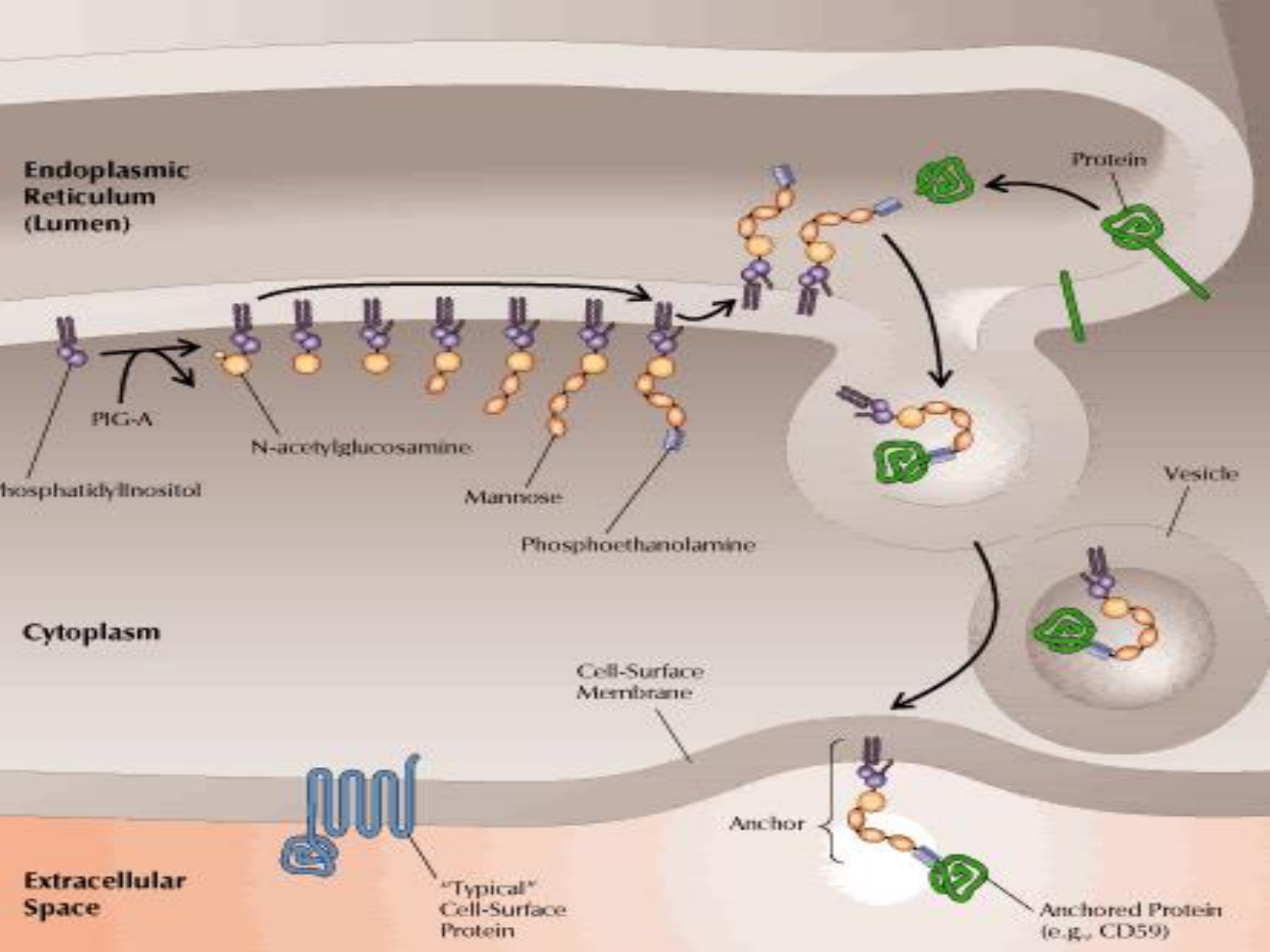
    that the protein attaches to

- **Common variable in all missing cell surface proteins is Glycophosphatidylinositol (GPI) anchor**

GPI anchor

- Unclear purpose
- Defective biosynthesis at early step
- Coded by the *PIG-A* gene
- Approx 30 GPI-anchored proteins; 20 shown to be deficient in PNH
- All vary greatly in function (enzymes, receptors, and complement mediators)




Endoplasmic Reticulum (Lumen)
Protein
PIG-A
N-acetylglucosamine
hosphatidylInositol
Mannose
Phosphoethanolamine
Vesicle
Cytoplasm
Cell-Surface Membrane
Anchor
Extracellular Space
"Typical" Cell-Surface Protein
Anchored Protein (e.g., CD59)

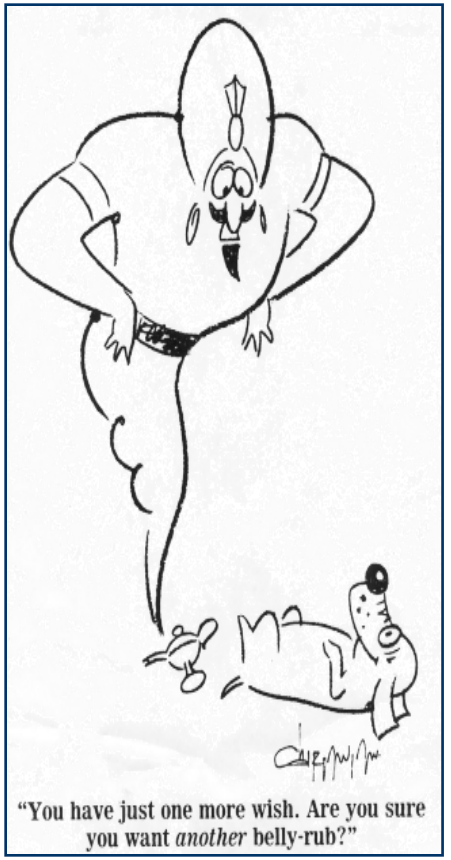
Missing proteins of importance

Complement regulating proteins:

- **CD59** (aka MAC inhibitor/protectin)
- **Homologous restriction factor** (HRF)
- **CD55** (aka decay accelerating factor)

Thrombosis regulating proteins:

- **CD87** (aka urokinase-type plasminogen activator receptor)



PNH Cell Types

- **Type I**: almost normal cells
- **Type II**: intermediate
- **Type III**: very sensitive
- Type II/III cells bind increased C3—excessive number of MAC are formed
- Can exist in any combination in pts with PNH

Clinical features

- **Highly variable**
- **Classic Triad**
  - Hemolytic Anemia
  - Bone Marrow failure (thrombocytopenia/neutropenia)
  - Venous Thrombosis
- **Chronic course with acute exacerbations**
- **Exacerbations often associated with infection**

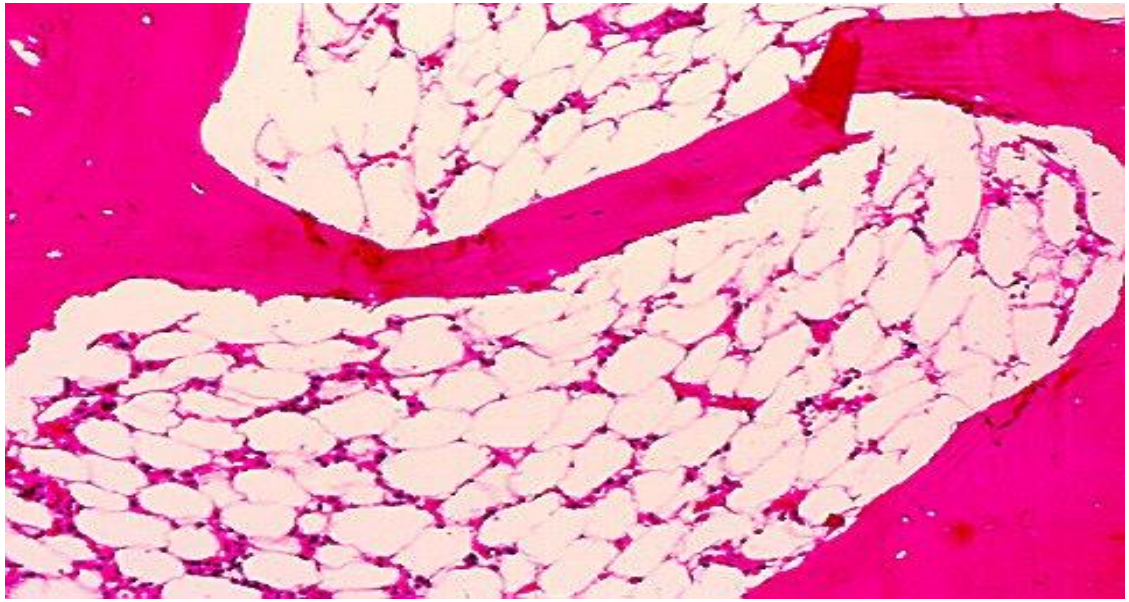
Hemolytic Anemia

- **Present to some degree in all cases**
- **Degree of hemolysis depends on:**
  - Proportion of sensitive RBCs
  - Cell type (PNH I-III)
  - Complement activation (ie infection, allergies, transfusion reaction, etc)

- **Other effects of hemolysis:**
  - Iron deficiency
  - ATN/ARF during episodes of massive hemolysis
  - CRF
  - Esophageal spasm (achalasia-like sx)
  - Impotence

Bone Marrow Failure

- Most severe: aplastic anemia
- More commonly: active BM producing defective cells
- 2/3 – thrombocytopenia/granulocytopenia



Venous Thromboses—the sinister sign

- 20% incidence in Europe and US (lower in Asians)
- Mainly central thromboses:
  - Liver (Budd-Chiari)
    - hepatic veins can thrombose in acute crisis or insidiously
    - Tends to persist with periodic exacerbations/remissions
    - Usually ultimately fatal
  - Cerebral Veins/Sinuses
    - Less common
    - Also tends to persist—Poor prognosis
  - Abdominal Veins
    - Renal/Spleen/Stomach/Intestinal
- LE DVT more common than in general population, but death by PE rare
- Arterial thrombosis also rare

Diagnosis

- Ham test (acidified-serum lysis test)
  - Gold standard from 1939 until advent of flow cytometry
  - Activation of complement by low pH; PNH cells lyse
  - High specificity
  - Cannot detect varying degrees of RBC sensitivity
- Flow Cytometry
  - Increased level of sensitivity: allows detection of 0.1% GPI-deficient clones
  - Uses monoclonal Ab to missing proteins (CD55/CD59) and fluorescence of labeled cells to detect certain cell populations
  - May screen RBCs, Platelets, and Lymphocyte components

Course and Prognosis

- Life span estimates 10-15yrs
- Approx 25% will survive > 25 yrs
- Spontaneous recovery in ~15% w/o long-term sequelae

Course and Prognosis

- Most common causes of death:
  - consequences of thrombosis (~33%)
  - effects of BM failure (~10%)
- May be preceded by or lead to the development of aplastic anemia (AA)
  - Incidence from various studies of 25-58%
  - Much less risk of thrombosis—less PNH cells overall
  - Possible “natural gene therapy” producing cells which escape destruction in the setting of AA
- 3-5% progress to acute leukemia
  - Likely more related to predisposition in pts with AA, not PNH itself

Treatment

- Focus on 3 aspects:
  - Treat anemia
  - Treat and prevent thromboses
  - Modification of hematopoiesis
- Mainly focused on control of complications rather than interrupting disease process

Treating Cytopenias

- PRBC/Platelet Transfusions
  - Replaces destroyed cells
  - Also suppresses erythropoiesis when done on chronic basis
  - Special transfusion considerations only if necessary
- Epogen/$FeSO^4$/Folate
  - Expensive, but shown to decrease need for high dose steroids and less transfusions
- Glucocorticoids
  - Unknown MOA
  - Useful in 50% pts
  - Thought to be related to direct prevention of hemolysis
  - 0.3-1 mg/kg/day

Treatment and Prevention of Clots

- Prevention
  - Prophylactic anticoagulation for pts w/o contraindications
- Treatment
  - IV/Oral anticoagulants
  - Thrombolytics:

    TPA/Streptokinase/Urokinase

Modifying Hematopoiesis

- **Immunosuppresants**
  - **Better response in pts with hypoplastic marrow than hemolysis**
  - **Mixed results: antithymocyte globulin response rates 0-63%; cyclosporin not effective**
- **Bone Marrow Transplant**
  - Currently most curative and optimal Tx
  - High risk of morbidity/mortality (10-20%)
  - Risk:benefit considering pts with lesser sx
  - No controlled studies for ethical reasons
- **Gene therapy**